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1649

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Phillip W. Berman; Laurence A. Lasky

Application No.: 08/459,141

Filed: 6/2/1995

For: **Immunogenic Composition Based on a Truncated Derivative of a Membrane Bound Protein And Process For Making It**

Examiner: Winkler, U.

Art Unit: 1648

APPEAL BRIEF

Commissioner for Patents
Alexandria, VA 22313

Dear Sir:

APPEAL BRIEF

Real Party in Interest.

The real party in interest in the present appeal is Genentech, Inc., the assignee of the above-referenced application.

Related Appeals and Interferences.

Appellants, Appellants' Attorney, and the assignee of the present application are unaware of any appeals or interferences that will directly affect, be directly affected by, or have a bearing on, the Board's decision in the present appeal, with the exception of an appeal in co-pending Application No. 08/470,107, filed June 6, 1995.

Status of Claims.

On June 11, 2003, Appellants appealed from the final rejection of claims 10-23 and 25-41. Originally filed claims 1-9 were cancelled in Paper No. 6. Claims 20-41 were added after filing, and claim 24 was cancelled in the Submission Under 37 C.F.R. § 1.129 and Amendment

(claim 24 was designated as claim 9 in this submission due to confusion over the claim numbering). Accordingly, all of the pending claims are rejected and on appeal.

Status of Amendments.

The claims were amended in response to the Office Action dated December 12, 2001. The claims were further amended in the Amendment dated January 23, 2004, which was filed in response to the Final Office Action (dated December 16, 2002). Accordingly, the appealed claims are the claims as amended in the January 23, 2004 amendment.

Summary of Invention.

Appellants' invention includes methods and compositions relating to a truncated, membrane-free derivative of a normally membrane-bound polypeptide, wherein the normally membrane-bound protein is characterized by a membrane-binding domain and antigenic determinants capable of raising neutralizing antibodies against *in vivo* challenge by a pathogen. Appellants' specification, page 4, line 21 to page 5, line 3. As recited in Claim 10, the derivative "is devoid of the membrane-binding domain," but still "has exposed antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by the pathogen." Applicants discovered that, surprisingly, the deletion of the membrane-binding domain did not abolish the ability of the derivative to elicit antibodies that bind to the native protein. Even more surprising, as demonstrated with the herpes glycoprotein D (gD), these antibodies were shown to neutralize infectivity of the pathogen. Appellants' specification, page 28, line 16 - page 29, line 20 and page 31, line 5 - page 32, line 4.

Claim 10 relates to an immunogenic composition comprising such a truncated, membrane-free derivative. Claim 14 relates to a method of producing the immunogenic composition and incorporates all of the elements of Claim 10 by reference to the immunogenic composition recited in claim 10. Claim 32 relates to a nucleic acid encoding a truncated, membrane-free derivative identical to that recited in claim 10, and claims 35 and 36 relate, respectively, to a vector comprising this nucleic acid and a host cell comprising the vector. Claim 39 relates to a method of producing an immunogenic composition that entails "culturing the host cell of claim 36; and . . . recovering the derivative from the culture." Claims 40 and 41 incorporate all of the elements of claim 10. All of the other pending claims depend from one of these claims. Thus, all of the pending

claims either recite or incorporate by reference the important feature of the invention described above, namely:

> An immunogenic composition comprising a truncated, membrane-free derivative of a polypeptide comprising a membrane-binding domain and antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by a pathogen, ***wherein said derivative:***
>
> ***(a) is devoid of the membrane-binding domain*** whereby the derivative is free of membrane, ***and***
>
> ***(b) has exposed antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by the pathogen*** . . .
>
> .

See claim 10 (emphasis added).

Applicants also established that the truncated derivative of a pathogen protein could be expressed in a stable eukaryotic cell line, such as a mammalian cell line, and recovered from the cell culture medium. Appellants' specification, lines 6-14. This secreted derivative of the pathogen protein unexpectedly retained the capability of eliciting antibodies that bind to the native protein and neutralize infectivity of the pathogen. Appellants' specification, page 28, line 16 - page 29, line 20 and page 31, line 5 - page 32, line 4. These features of the invention are recited in claims 15 and 16, relating to production methods; claims 27 and 28, relating to immunogenic compositions; and claims 36-8, relating to vectors.

The appealed claims are set forth in Appendix A.

Issues.

In the Final Office Action (dated December 16, 2003), claims 10-12, 14-19, 25-29, and 32-41 were rejected under the judicially created doctrine of obviousness-type double patenting over claims 13, 19, and 20 of U.S. Patent No. 4,855,224 (issued August 8, 1989 to Berman *et al.*). Final Office Action (dated December 16, 2003), pages 3-4.

Claims 10-23 and 25-41 (*i.e.*, all pending claims) were rejected for obviousness-type double patenting over claims 13, 19, and 20 of the '224 patent in view of Watson *et al.* (Science

1982, 218:381-84)[1] and Dundarov *et al.* (Develop. Biol. Standard. 1982, 52:351-58). Final Office Action (dated December 16, 2003), pages 4-5.

Grouping of Claims.

The pending claims do not stand or fall together. In particular, claims 10, 11, 14-19, 25-29, and 32-41 stand or fall together. Claims 12, 13, 30, and 31 are separately patentable; and Claims 20-23 are separately patentable.

Argument.

I. The rejection of claims 10-12, 14-19, 25-29, and 32-41 for obviousness-type double patenting over the '224 patent is improper.

A. The rejection.

Claims 10-12, 14-19, 25-29, and 32-41 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 13, 19, and 20 of the '224 patent. As noted above, the pending claims all either recite or refer to a derivative of a membrane polypeptide that:

> ***(a) is devoid of the membrane-binding domain*** whereby the derivative is free of membrane, ***and***
>
> ***(b) has exposed antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by the pathogen*** . . .

Claim 13 of the '224 patent recites:

A diagnostic test kit comprising:

> (a) a diagnostic product comprising ***a membrane-bound polypeptide with antigenic determinants capable of specifically binding complementary antibodies to herpes simplex virus***, said polypeptide being formed in a recombinant, stable, continuous cell line; and

[1] The Final Office Action identified the Watson reference as "Watson et al (Science 1992)." However, in a telephone conference, Examiner Winkler confirmed that reference cited was actually the 1982 Science article authored by Watson.

> (b) a second component comprising either said complementary antibody or anti-antibody capable of specifically binding said complementary antibody.

(Emphasis added.) Claim 19 depends from claim 13 and recites that the "diagnostic product is a truncated, membrane-free derivative of a polypeptide," said derivative ***being "devoid of a membrane-binding domain*** whereby the derivative is free of said membrane." Claim 20 depends from claim 19 and recites that "the truncated polypeptide is formed by secretion from a recombinant eukaryotic host cell system."

The obviousness-type double patenting rejection appeared in the First Office Action (dated March 15, 2002). In the Response dated September 16, 2002, Appellants argued as follows:

> The Examiner stated that the "patented claims are drawn to diagnostic products, which have the same structure as the instantly claimed immunogenic composition." Office Action, page 6. However, Applicants submit that the pending claims recite at least one structural-functional element that clearly distinguishes the claims of the . . . ['224] patent. Specifically, the pending claims recite "a truncated, membrane-free derivative of a polypeptide . . . [that] has exposed antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by the pathogen." *See* claim 10. By contrast, the claims of the . . . ['224] patent relate to polypeptides "capable of specifically binding complementary antibodies." *See* claim 13. Thus, the claims of the . . . ['224] patent do not require the presence of ***neutralizing*** antigenic determinants. That it is possible to produce a truncated, membrane-free derivative of a polypeptide that retains the ability to ***bind*** complementary antibodies suggests nothing regarding the possibility of producing a truncated, membrane-free derivative that has the ability to ***raise neutralizing*** antibodies ***in vivo***. This difference in the requirements for how the truncated polypeptide functions reflect different structural requirements because, as the Examiner has pointed out, "[c]hemical compounds and their functions are inseparable." Office Action, page 7. Thus, the claims of the present application incorporate a structural-functional requirement that is not suggested by the claims of the . . . ['224] patent.

Response (dated September 16, 2002), pages 6-7.

The Examiner responded to this argument in the Final Office Action, stating:

> In the instant rejection, the structure of the prior patent is the same as that in the present invention, adding the descriptive phrase "capable of raising neutralizing antibodies *in vivo*" has not altered the structure of the composition. Because antibodies recognize structure, the prior

> patent structure is the same as the present structure and therefore meets the limitation of "capable of raising neutralizing antibodies *in vivo*."

Final Office Action (dated December 16, 2002), page 4. The "structure" relied on by the Examiner is a truncated form of the herpes simplex virus (HSV) glycoprotein D (gD). *See* First Office Action (dated March 15, 2002), pages 6-7. This HSV gD derivative was disclosed in the '224 patent as an example of the diagnostic product recited in claims 13, 19, and 20. The disclosed gD derivative is capable of raising neutralizing antibodies *in vivo*. The Examiner's position is that this property is inherent in the structure of the derivative and cannot therefore distinguish the invention claimed in the present application from the diagnostic kit recited in claims 13, 19, and 20 of the '224 patent. Appellants respectfully submit that the Examiner arrives at this conclusion only by treating the specification of the'224 patent as prior art *vis a vis* the present application. Such treatment is not permitted in the context of an obviousness-type double patenting analysis.

B. The governing law: *In re Vogel.*

Appellants and the Examiner agree that this analysis is governed by *In re Vogel*, 422 F.2d 438 (C.C.P.A. 1969). In this case, the court stated that the question to be answered in analyzing obviousness-type double patenting was: "Does any claim in the application define merely an obvious variation of an invention disclosed and claimed in the patent?" *Id.* at 441. The court cautioned that "[i]n considering the question, the patent disclosure may not be used as prior art." *Id.* In *Vogel*, the court found that the "disclosure . . . sets forth at least one tangible embodiment within the claim, and it is less difficult and more meaningful to judge whether that thing has been modified in an obvious manner." *Id.* at 442. The court emphasized that "only the disclosure of the invention claimed in the patent may be examined." *Id.* In accordance with this requirement, it is necessary to "determine how much of the patent disclosure pertains to the invention claimed in the patent." *Id.* In *Vogel*, the claims recited a method for processing pork. The court determined how much of patent disclosure could be considered in connection with the obviousness-type double patenting rejection as follows:

> The specification begins with certain broad assertions about meat sausages. These assertions do not support the patent claims. The patent claims recite "pork" and "pork" does not read on "meat." To consider these broad assertions would be using the patent as prior art, which it is not. The specification then states how the process is to be

> carried out with pork. This portion of the specification supports the patent claims and may be considered.

Id.

C. None of the pending claims recites an obvious variation of the diagnostic kit recited in claims 13, 19, and 20 of the '224 patent.

Applying this analysis in the present application, the claims of the '224 patent recite a diagnostic kit. The kit contains "a diagnostic product comprising a membrane-bound polypeptide with antigenic determinants capable of specifically binding complementary antibodies to herpes simplex virus" and an antibody. The pending claims, by contrast, do not recite a diagnostic kit and do not require the presence of an antibody. Rather, the pending claims recite an immunogenic composition and related compositions and methods, all of which incorporate the concept of a derivative of a membrane-bound polypeptide that "is devoid of the membrane-binding domain whereby the derivative is free of membrane, and . . . ***has exposed antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by . . . [a] pathogen***." To analyze obviousness-type double patenting, then, it is necessary first to answer the question: "Is an immunogenic composition containing a polypeptide derivative capable of eliciting an *in vivo* neutralizing antibody response against a pathogen merely an obvious variation of a diagnostic kit containing: (1) a polypeptide derivative that is capable of specifically binding complementary antibodies to herpes simplex virus and (2) an antibody?" Without resort the specification of the '224 patent, the answer to this question is clearly "no."

More specifically, to establish a *prima facie* case of obviousness, the Examiner must demonstrate that (1) all elements of the invention are found in the cited art; (2) the cited art provided motivation to combine or, if necessary, modify these elements to arrive at the claimed invention; and (3) the cited art revealed that, in making the claimed invention, those of ordinary skill in the art would have a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

As stated above, the knowledge that a polypeptide derivative can bind complementary antibody does not suggest that the derivative can elicit an *in vivo* neutralizing antibody response. Accordingly, all elements of the invention are not found in the claims of the '224 patent. Moreover, the knowledge that a polypeptide derivative is useful as a component of a diagnostic kit does not suggest that it can be used as an immunogen. The record is devoid of any reason why one skilled in

the art would omit the antibody from the kit recited in the claims of the '224 patent and use the "diagnostic product" recited therein as an immunogen. Therefore, the claims of the '224 patent fail to provide any motivation to modify the recited kit to produce the immunogenic composition of the claimed invention. Furthermore, even if some motivation could be found for this modification, the claims of the '224 patent provide no assurance that the recited diagnostic product would be a satisfactory immunogen, much less one capable of eliciting an *in vivo* neutralizing antibody response that protects against pathogen.

Accordingly, none of the pending claims recites an obvious variation of the diagnostic kit recited in claims 13, 19, and 20 of the '224 patent, when one considers only these '224 patent claims.

D. None of the pending claims recites an obvious variation of the diagnostic kit described in portions of the '224 specification that support claims 13, 19, and 20 of the '224 patent.

The next question in the analysis then is: Does some portion of the '224 specification that discloses the diagnostic kit recited in claims 13, 19, and 20 of the '224 patent suggest the immunogenic composition of the claimed invention? Appellants submit that this question can be considered most efficiently by determining whether any portions of the '224 specification that relate to an immunogenic composition that elicits an *in vivo* neutralizing antibody response provide support for the diagnostic kit.

At col. 2, line 56 - col. 3, line 8, the '224 patent states:

> In the light of this information about the structure of the gD protein, as described more fully herein, it was decided to express the gD protein DNA in mammalian cells to see whether such was possible, and if possible, whether the expressed protein would bind to the host cell membrane, and whether a truncated form of protein lacking the membrane-binding domain would be secreted from the host cell, and in either of the latter cases whether the expression product proteins could bind with antibodies effective against HSV-1 and/or HSV-2. This procedure is fully described in copending application Ser. No. 527,917, filed Aug. 30, 1983, incorporated herein by reference. As shown in that application, such expression product proteins are capable of raising antibodies effective against HSV-1 and/or HSV-2 and are thus useful as a vaccine. As the results herein will show, such expressed proteins obtained by recombinant DNA processes, being capable of recognition by antibodies against HSV-1 and/or HSV-2,

> also are useful diagnostic products for detecting and/or measuring the presence of antibodies characteristic of those viruses.

In the above passage, the only sentence that addresses the use of gD as an immunogen is the sentence: "As shown in that application, such expression product proteins are capable of raising antibodies effective against HSV-1 and/or HSV-2 and are thus useful as a vaccine." Applying the *Vogel* analysis, the described use of recombinant gD as an immunogen does not support the '224 patent claims, which recite a diagnostic kit. The patent claims do not read on an immunogenic composition *per se* (because they also require the presence of antibody). The specification goes on to state that recombinant gD is useful as a diagnostic product. This portion of the specification supports the patent claims and may be considered. However, this teaching does not, in any way, suggest the claimed invention.

Example 3 of the '224 specification describes the expression of a truncated gD that lacks the membrane-binding domain. This example contains a general description of recombinant expression of the truncated gD ('224 Patent, col. 17, line 45 - col. 20, line 27), followed by a section entitled "Preparation of Truncated gD Used for Immunization" ('224 Patent, col. 20, lines 28-50). This section describes the preparation of a truncated gD that lacks the membrane-binding domain and states: "The preparation was then dialyzed extensively against phosphate buffered saline (PBS) and used for immunization without further purification." *Id.* at col. 20, lines 47-50. Example 3 goes on to state:

> The success of this invention in demonstrating that a truncated form of a membrane bound protein, lacking that part of the hydrophobic-hydrophilic carboxy-terminal region responsible for binding it to the membrane, can yet be immunogenic indicates that similar results can be expected with other immunogenic membrane bound proteins, thus providing an improved source of vaccine against viruses, parasites and other pathogenic organisms.

Id. at col. 21, line 66 - col. 22, line 6. This section of the '224 specification does not support the patent claims to a diagnostic kit. The general description of the truncated gD that precedes this section provides ample support for the patent claims and may be considered in connection with the obviousness-type double patenting analysis. However, there is nothing in this general description that teaches or suggest to one skilled in the art that the truncated gD would be useful as an immunogen, much less one capable of eliciting an *in vivo* neutralizing antibody response. Col. 19, lines 40-42 states that the "protein was extracted from the medium and the cells were tested for

immunogenic activity." However, the next sentence describes the results of immunoprecipitation studies, demonstrating that the truncated gD was immunoprecipitated by anti-HSV-1 antiserum. These studies showed that the truncated gD was capable of binding complementary antibody, which says nothing about this derivative's ability to elicit an antibody response.

That the above analysis is correct is clear in light of *In re Kaplan*, 789 F.2d 1574 (Fed. Cir. 1986). In that case, the claim rejected for obviousness-type double patenting related to a chemical process carried out in a solvent mixture of tetraglyme and sulfolane. *Id.* at 1575. The reference (Kaplan) patent claimed the same process carried out "in the presence of an organic solvent." *Id.* The specification of the Kaplan patent included Example 45, which disclosed carrying out the process in a mixture of tetraglyme and sulfolane. *Id.* Thus, the case turned on whether Example 45 provided support for the "organic solvent" element of the Kaplan patent claims, allowing this example to be considered in evaluating obviousness-type double patenting of the later application. The Board of Patent Appeals and Interferences found that "Example 45 of the Kaplan patent clearly shows that the term solvent, as used in Kaplan's claims is intended to *embrace* the mixed solvent of Example 45" and upheld the obviousness-type double patenting rejection. *Id.* at 1576. In justifying this view, the Board reasoned that the tetraglyme/sulfolane solvent "*provides some of the support* for the term 'organic solvent' as used in claim 4 of the Kaplan patent." *Id.* at 1577. The Federal Circuit reversed, stating:

> There is adequate support for the "organic solvent" limitation in claim 4 apart from appellants' specific mixed solvent invention, including the disclosure of the separate solvents in the mixture which are separately claimed by Kaplan. There is no way the board could have found appellants' claimed invention to be an obvious variation of what Kaplan claims except by treating the Kaplan patent disclosure as though it were prior art. This has repeatedly been held in our precedents to be impermissible.

Id. at 1580 (citations omitted). By the same token, there is adequate support for the diagnostic product recited in the claims of the '224 apart from statements concerning the immunogenicity of a particular example of this diagnostic product (gD). Consideration of such statements in the context of obviousness-type double patenting treats the '224 patent as if it were prior art, which the Federal Circuit has repeatedly held is improper.

Therefore, the answer to the question posed above is: No portion of the '224 specification that can be considered to disclose the diagnostic kit recited in claims 13, 19, and 20 of the '224 patent suggests the immunogenic composition of the claimed invention.

E. The obviousness-type double patenting rejection is improper because of the failure to establish (1) any motivation to modify the diagnostic kit recited in claims 13, 19, and 20 of the '224 patent to arrive at the claimed invention and (2) any reasonable expectation that such modification would succeed.

The Examiner bases the obviousness-type double patenting rejection on the contention that the truncated gD described in Example 3 inherently possesses the ability to elicit a neutralizing antibody response and that the mere description of the truncated gD renders the claimed invention obvious. *See* First Office Action (dated March 15, 2002), pages 6-7. This rationale is flawed for at least two reasons.

First, the rationale overlooks that fact that the claims 13, 19, and 20 recite a diagnostic kit, rather than a polypeptide derivative. The record is devoid of any reason why one skilled in the art would be motivated to use any component of the diagnostic kit for some purpose other than diagnosis. It is well-settled that a *prima facie* case requires ***specific*** motivation to produce the invention. The Federal Circuit emphasized the necessity for finding specific motivation in *In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998). There, the court stated:

> "[V]irtually all [inventions] are combinations of old elements." *Environmental Designs, Ltd. v. Union Oil Co., 713 F.2d 693, 698, 218 U.S.P.Q. 865, 870 (Fed. Cir. 1983)*; *see also Richdel, Inc. v. Sunspool Corp., 714 F.2d 1573, 1579-80, 219 U.S. P.Q. 8, 12 (Fed. Cir. 1983)* ("Most, if not all, inventions are combinations and mostly of old elements."). Therefore an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be "an illogical and inappropriate process by which to determine patentability." *Sensonics, Inc. v. Aerosonic Corp., 81 F.3d 1566, 1570, 38 U.S.P.Q. 2d 1551, 1554 (Fed. Cir. 1996).*

Id. at 1357. The court then noted that the Board had failed to "explain what ***specific*** understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested" the invention. *Id.* (emphasis added). In the present case, the only specific understanding that could have lead one skilled in the art to disassemble the kit recited in '224 patent claims 13, 19, and 20 and use a component of that kit as an immunogen is the knowledge that the component was, in fact, immunogenic. The only teaching or suggestion that the claimed component is immunogenic is found in portions of the '224 specification than may not be considered in the context of an obviousness-type double patenting rejection. Thus, motivation for modifying claims 13, 19, and 20 to arrive at the claimed invention can be found only by using the '224 patent as prior art, which is clearly impermissible. Accordingly, the record fails to properly establish the second element of a *prima facie* case of obviousness. The record is similarly deficient with respect to the third element of a *prima facie* case. Without resort to portions of the '224 specification that cannot properly be considered in the present context, there is no reasonable assurance that the "diagnostic product" recited in claims 13, 19, and 20 is capable of eliciting an *in vivo* neutralizing antibody response, as required by all of the pending claims.

F. The obviousness-type double patenting rejection is improper because obviousness cannot be predicated on inherency.

The second flaw in the rationale underlying the rejection is that inherency cannot, without more, be relied upon to establish obviousness. As the Federal Circuit stated in *In re Rijckaert*, 9 F.3d 1531 (Fed. Cir. 1993):

> "That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown."

Id. at 1534 (citation omitted). Applying this rule to the present case, the portions of the '224 specification that are available for consideration for obviousness-type double patenting purposes contain no suggestion of disassembling the kit recited in '224 patent claims 13, 19, and 20 and using the polypeptide derivative component of the kit in an immunogenic composition. That the truncated gD exemplifying the polypeptide derivative was capable of eliciting an *in vivo* neutralizing antibody response is irrelevant to the present inquiry because one skilled in the art would not have known this from reading the portions of the specification that support the claims 13, 19, and 20 of the '224 patent. Properties of the truncated gD that are inherent, but neither disclosed nor suggested in any

portion of the '224 specification that can be considered, cannot be relied upon to establish obviousness.

Because rejected claims 10-12, 14-19, 25-29, and 32-41 recite subject matter that is not an obvious variation of the diagnostic kit recited in claims 13, 19, and 20 of the '224 patent, the obviousness-type double patenting rejection of these claims is improper. Reversal of this rejection is respectfully requested.

G. Claim 12 is separately patentable over claims of the '224 patent.

As stated above, the obviousness-type double patenting rejection is based on the '224 specification's disclosure of a truncated gD as an example of the polypeptide derivative recited in claims 13, 19, and 20 of the '224 patent.

Claim 12 of the present application recites an immunogenic composition wherein the polypeptide derivative "is a derivative of glycoprotein C." Appellants can find no indication in the record as to why, considering only the '224 patent, an immunogenic composition comprising a truncated gC that is capable of eliciting an *in vivo* neutralizing antibody response is considered to be an obvious variation of the kit recited in claims 13, 19, and 20 of the '224 patent. The explanations of the rejection appearing in the First and Final Office Actions (dated March 15, 2002 and December 16, 2002, respectively) shed little light on this question. The only basis for the rejection appears to be that truncated gD is inherently capable of eliciting a neutralizing antibody response and that a similarly truncated gC would be as well. However, as explained above, this inherent property of gD is not disclosed in any portion of the specification available for consideration for obviousness-type double patenting purposes. Therefore, this property of truncated gD must be taken as unknown. An unknown property of one glycoprotein cannot be extrapolated to another glycoprotein.

Moreover, assertions regarding the immunogenicity of polypeptide derivatives within the scope of claims 13, 19, and 20 of the '224 patent must be disregarded in determining obviousness-type double patenting, as such assertions do not provide support for the claims. In the absence of any information regarding the immunogenicity of truncated gC, there is no reason that one skilled in the art would disassemble the kit recited in '224 patent claims 13, 19, and 20 and use a component of that kit as an immunogen. One skilled in the art would have had no motivation to do

so and no reasonable expectation of success in producing an immunogen capable of eliciting an *in vivo* neutralizing antibody response. As stated above, obviousness cannot be predicated on inherency, especially when the inherent property concerned is inherent in a different polypeptide derivative (gD) than that recited in claim 12 (gC). Accordingly, for this additional reason, claim 12 recites subject matter that is not an obvious variation of the diagnostic kit recited in claims 13, 19, and 20 of the '224 patent.

Thus, claim 12 is separately patentable over claims 13, 19, and 20 of the '224 patent. Reversal of the obviousness-type double patenting rejection of claim 12 is therefore respectfully requested.

II. The rejection of claims 10-23 and 25-41 for obviousness-type double patenting over the '224 patent in view of Watson and Dundarov is improper.

A. The rejection.

Claims 10-23 and 25-41 (all pending claims) stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 13, 19, and 20 of the '224 patent in view of Watson *et al.* and Dundarov *et al.*

B. Neither Watson nor Dundarov remedy the deficiencies of the '224 patent.

Watson discloses the cloning and expression of the HSV-1 gD in bacteria. Watson, abstract. Watson teaches a putative membrane-binding domain at amino acid positions 340-364. *Id.* at page 382, col. 2, second full paragraph. Watson expressed a gD polypeptide that lacked only the N-terminal 52 amino acids and thus included the putative membrane-binding domain. *Id.* at page 383, col. 1, first full paragraph. Watson expressed a second polypeptide containing "the gD coding region." *Id.* at page 383, col. 2-3. Thus, neither polypeptide lacked the membrane-binding domain as recited in the pending claims. Therefore, Watson necessarily fails to teach or suggest that a gD polypeptide lacking this domain would be capable of eliciting an *in vivo* neutralizing antibody response. Accordingly, Watson fails to provide any motivation for disassembling the kit recited in '224 patent claims 13, 19, and 20 and using a component of that kit, such as truncated gD, as an immunogen. Nor does Watson provide any reasonable assurance that, if one did so, the truncated gD could elicit an *in vivo* neutralizing antibody response. Furthermore, nothing in Watson would

allow one skilled in the art to recognize any properties inherent in the truncated gD described in the portions of the '224 specification that are available for consideration in connection with obviousness-type double patenting. Thus, Watson fails to remedy the deficiencies in the obviousness-type double patenting rejection based on the '224 patent alone.

Dundarov is even less relevant. Dundarov reports on the efficacy and safety of inactivated herpes vaccines. Dundarov, abstract. Dundarov contains no mention of a truncated polypeptide of any type that lacks a membrane-binding domain. Thus, Dundarov suffers from the same failings as Watson.

Because rejected claims 10-23 and 25-41 recite subject matter that is not an obvious variation of the diagnostic kit recited in claims 13, 19, and 20 of the '224 patent, the obviousness-type double patenting rejection of these claims is improper. Reversal of this rejection is respectfully requested.

C. Claims 12, 13, 20-23, 30, and 31 are separately patentable over the '224 patent in view of Watson and Dundarov.

Claims 12 and 13 of the present application recite an immunogenic composition wherein the polypeptide derivative is "a derivative of glycoprotein C" or "a derivative of glycoprotein B," respectively. Claims 20-23 recite that the "immunogenic composition comprises a mixture of glycoproteins or glycoprotein derivatives." Claims 30 and 31 relate to a method of producing an immunogenic composition that comprises a truncated gC or gB, respectively. Thus, each of these claims recites an immunogenic composition including something other than a truncated gD alone.

The Examiner contends that Watson and/or Dundarov render the elements recited in these claims obvious. In particular, the Examiner notes:

> The patented claims [of the '224 patent] do not teach HSV gB. However, the production of [an] HSV gB immunogenic composition would be obvious over the patented claims in view of Watson et al., [as] the reference teaches that HSV glycoproteins A-E are known and that antibodies to all of the glycoproteins are capable of neutralizing infection (see Watson column 1, 2nd paragraph).

* * *

> The patented claims also do not each a polyvalent mixture of the immunogenic compositions, however, a combinations [*sic*] of the teachings in Watson et al. which indicates that neutralizing antibodies are made to all glycoproteins and the teaching in Dundarov et al. which [discloses] use of polyvalent HSV vaccine for producing an immune resposne [*sic*] in a host [*sic-sentence fragment in original*]. Therefore, the instant invention drawn to an immunogenic composition comprising HSV gB, gC and gD and combinations thereof (polyvalent) . . . is obvious over the U.S. Patent No. 4,855,224 in view of Watson et al. and Dundarov et al.

First Office Action (dated March 15, 2002), pages 8-9.

The teaching in Watson cited by the Examiner is that "[a]ntiserums [*sic*] to each of these glycoproteins can neutralize infectivity of the homologous HSV type in an in vitro assay." This teaching does not, as the Examiner appears to believe, establish that these glycoproteins possess "antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by a pathogen," which is an element of all of the pending claims. Neutralization of infectivity *in vitro* is not necessarily predictive of *in vivo* neutralization.

Moreover, this teaching says nothing about the ability of a truncated derivative of any of the herpes glycoproteins to elicit an *in vivo* neutralizing antibody response. For this element of the invention, the Examiner relies on the inherent ability of the truncated gD disclosed in the '224 patent to elicit this response. However, as explained above, this inherent property of gD is not disclosed in any portion of the specification available for consideration for obviousness-type double patenting purposes. Therefore, this property of truncated gD must be taken as unknown. An unknown property of one glycoprotein cannot possibly suggest that other glycoproteins would have that property. The obviousness of claims reciting truncated gB or gC cannot be predicated on an undisclosed, though inherent, property of gD. *See In re Rijckaert*, 9 F.3d 1531 (Fed. Cir. 1993). Accordingly, claims 12, 13, 30, and 31 cannot be considered to recite obvious variations of the diagnostic kit recited in claims 13, 19, and 20 of the '224 patent, even taken with Watson and/or Dundarov.

Dundarov is concerned with *in vivo* responses, but the immunization of inactivated herpes virus tells one nothing about the results that would be achieved upon immunization with a mixture of individual herpes glycoproteins, much less one including a truncated derivative of these glycoproteins. The Examiner emphasizes the "polyvalence" of the Dundarov vaccines as teaching mixtures of individual glycoproteins, but Dundarov does not use this term as suggested by the

Examiner. Rather, Dundarov's polyvalent vaccines contained inactivated virus from 5 or more different strains of HSV-1 and HSV-2. *See* Dundarov, page 351, second paragraph. Thus, Dundarov teaches the mixing of whole virus from multiple different strains to produce polyvalent vaccines. This teaching does not suggest mixing individual herpes glycoproteins, at least one of which is truncated. For this additional reason, claims 20-23 cannot be considered to recite obvious variations of the diagnostic kit recited in claims 13, 19, and 20 of the '224 patent, even taken with Watson and/or Dundarov.

Thus, claims 12, 13, 20-23, 30, and 31 are separately patentable over the '224 patent in view of Watson and Dundarov. Reversal of the obviousness-type double patenting rejection of claims 12, 18, 20-23, 30, and 31 is therefore respectfully requested.

Conclusion

Appellants submit that the Examiner's rejection of claims 10-12, 14-19, 25-29, and 32-41 for obviousness-type double patenting over the '224 patent is improper. Appellants further submit that the rejection of claims 10-23 and 25-41 for obviousness-type double patenting over the '224 patent in view of Watson and Dundarov is also improper. Withdrawal of these rejections by the Examiner or reversal by the Board is respectfully requested.

The Commissioner is authorized to charge the fee under 37 C.F.R. § 1.17(c) and any other required fees, or to credit any overpayments, to Deposit Account No. 50-0893. This paper is submitted in triplicate.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3509.

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Attachments:

(1) Appendix A – Appealed Claims for 08/459,141

APPENDIX A

APPEALED CLAIMS FOR 08/459,141

1-9. (Cancelled)

10. (Previously Presented) An immunogenic composition comprising a truncated, membrane-free derivative of a polypeptide comprising a membrane-binding domain and antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by a pathogen, wherein said derivative:

(a) is devoid of the membrane-binding domain whereby the derivative is free of membrane, and

(b) has exposed antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by the pathogen.

11. (Previously Presented) An immunogenic composition according to Claim 25 wherein the derivative is a derivative of glycoprotein D.

12. (Previously Presented) An immunogenic composition according to Claim 25 wherein the derivative is a derivative of glycoprotein C.

13. (Previously Presented) An immunogenic composition according to Claim 25 wherein the derivative is a derivative of glycoprotein B.

14. (Previously Presented) A method of producing an immunogenic composition according to any one of Claims 10, 11, 12, or 13, said method comprising preparing a nucleic acid encoding said derivative, incorporating said nucleic acid into an expression vector, introducing said vector into a host cell, and collecting the derivative as a secretion product.

15. (Previously Presented) A method according to Claim 14 wherein the host cell is a stable eukaryotic cell line.

16. (Previously Presented) A method according to Claim 15 wherein the host cell is a mammalian cell line.

17. (Previously Presented) A method according to Claim 15 wherein the cell line is deficient in the production of dhfr and the vector contains a dhfr selectable marker.

18. (Previously Presented) A method according to Claim 14 wherein the derivative is a derivative of glycoprotein D of herpes simplex virus type 1 or type 2.

19. (Previously Presented) A method according to Claim 18 wherein the derivative comprises the first 300 amino acid residues of the glycoprotein D.

20. (Previously Presented) An immunogenic composition according to Claim 25 wherein said immunogenic composition comprises a mixture of glycoproteins or glycoprotein derivatives.

21. (Previously Presented) An immunogenic composition according to Claim 20 wherein said mixture comprises glycoprotein C or a derivative thereof and glycoprotein D or a derivative thereof.

22. (Previously Presented) An immunogenic composition according to Claim 20 wherein said mixture comprises glycoprotein D or a derivative thereof.

23. (Previously Presented) An immunogenic composition according to Claim 22 wherein said mixture further comprises glycoprotein B or a derivative thereof.

24. (Cancelled)

25. (Previously Presented) An immunogenic composition according to Claim 10 wherein the derivative is a derivative of a herpes glycoprotein.

26. (Previously Presented) An immunogenic composition according to Claim 25 wherein the derivative is a derivative of a glycoprotein of herpes simplex virus type 1 or type 2, and the pathogen is herpes simplex type 1 and/or type 2.

27. (Previously Presented) An immunogenic composition according to Claim 25 wherein said derivative is produced in a stable eukaryotic cell line.

28. (Previously Presented) An immunogenic composition according to Claim 27 wherein said cell line is a mammalian cell line.

29. (Previously Presented) An immunogenic composition according to Claim 11 wherein said derivative comprises the first 300 residues of glycoprotein D.

30. (Previously Presented) A method according to Claim 14 wherein the derivative is a derivative of glycoprotein C of herpes simplex virus type 1 or type 2.

31. (Previously Presented) A method according to Claim 14 wherein the derivative is a derivative of glycoprotein B of herpes simplex virus type 1 or type 2.

32. (Previously Presented) A nucleic acid encoding a truncated, membrane-free derivative of a polypeptide comprising a membrane-binding domain and antigenic determinants

capable of raising neutralizing antibodies against in vivo challenge by a pathogen, wherein said derivative:

(a) is devoid of the membrane-binding domain whereby the derivative is free of membrane, and

(b) has exposed antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by the pathogen.

33. (Previously Presented) The nucleic acid of Claim 32 wherein the derivative is a derivative of a herpes glycoprotein.

34. (Previously Presented) The nucleic acid of Claim 33 wherein the derivative is a derivative of a glycoprotein of a herpes simplex virus type 1 or type 2, and the pathogen is herpes simplex type 1 and/or type 2.

35. (Previously Presented) An expression vector comprising a nucleic acid according to Claim 32.

36. (Previously Presented) A stable host cell comprising an expression vector according to Claim 35.

37. (Previously Presented) A host cell according to Claim 36 wherein the host cell is a eukaryotic cell.

38. (Previously Presented) A host cell according to Claim 37 wherein the host cell is a mammalian host cell.

39. (Previously Presented) A method of producing a truncated, membrane-free derivative of a polypeptide comprising a membrane-binding domain and antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by a pathogen, said method comprising:

(a) culturing the host cell of Claim 36; and

(b) recovering the derivative from the culture.

40. (Previously Presented) An immunogenic composition comprising a truncated, membrane-free derivative of a polypeptide comprising a membrane-binding domain and antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by a pathogen, wherein said derivative:

(a) is devoid of the membrane-binding domain whereby the derivative is free of membrane, and

(b) has exposed antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by the pathogen, wherein the pathogen is a virus.

41. (Previously Presented) An immunogenic composition comprising a truncated, membrane-free derivative of a polypeptide comprising a membrane-binding domain and antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by a pathogen, wherein said derivative:

(a) is devoid of the membrane-binding domain whereby the derivative is free of membrane, and

(b) has exposed antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by the pathogen, wherein said pathogen is a virus selected from the group consisting of herpes virus, influenza virus, foot and mouth disease virus, hepatitis virus, vesicular stomatitis virus and rabies virus.